REMARKS

Applicant requests reconsideration of the application in view of the foregoing amendments and the discussion that follows. The status of the claims is as follows. Claims 41-97 were previously canceled without prejudice to Applicant's filing of divisional applications to the separately patentable subject matter thereof and Claim 26 was previously canceled. Claims 1, 5, 7, 9, 15-18, 20, 21, 28, 29 and 98-101 stand rejected and Claims 2-4, 6, 8, 10-14, 19, 22-27 and 30-40 stand objected to. Claim 28 was amended herein and Claims 102-147 were added.

The Amendment

Claim 28 was amended to recite that the absolute value of the correlation coefficient between the two parameters is less than 0.5. Support therefor is in the Specification, for example, page 50, lines 46-47.

Claim 102 was added and is based on Claims 1 and 2. Claims 103-121 were added and depend ultimately from Claim 102 and find support in original Claims 3-40.

Claim 122 was added and is based on Claims 1 and 3. Claims 123-141 were added and ultimately depend from Claim 122 and find support in original Claims 1 and 3.

Claim 142 was added and depends from Claim 102 and finds support in original Claim 98. Claim 143 was added and depends from Claim 142 and finds support in original Claim 99.

Claim 144 was added and depends from Claim 122 and finds support in original Claim 98. Claim 145 was added and depends from Claim 144 and finds support in original Claim 99.

Claim 146 was added and is based on original Claims 100 and 2. Claim 147 was added and depends from Claim 146 and finds support in original Claim 101.

Terminal Disclaimer

Applicant acknowledges the Examiner's prior indication that the Terminal Disclaimer filed October 3, 2003, was approved.

Rejection under 35 U.S.C. §112

Applicant submits that the above amendment to Claim 28 obviates this ground of rejection.

Rejection under 35 U.S.C. §102

Claims 1, 5, 7, 9 15, 17, 18, 20, 21, 98 and 100 were rejected under paragraph (b) of the above code section as being anticipated by Mitsuhashi, *et al.* (U.S. Patent No. 5,556,749) (Mitsuhashi). Mitsuhashi discloses a computerized method for the design of oligonucleotide probes based on the GenBank database of DNA and mRNA sequences and the examination of candidate probes for specificity of commonality with respect to a user-selected experimental preparation. Two models are available: a Mismatch Model that employs hashing and continuous seed filtration and a H-Site Model that analyzes candidate probes for their binding specificity relative to some known set of mRNA or DNA sequences.

Mitsuhashi does not anticipate the claimed methods because, among others, Mitsuhashi does not disclose Applicant's claimed steps of forming clusters and selecting, for a cluster, a hybridization oligonucleotide wherein the hybridization of the hybridization oligonucleotide is predicted by the presence of the hybridization oligonucleotide in the cluster. Therefore, Mitsuhashi does not disclose each and every element of the claimed invention. Accordingly, a *prima facie* case of anticipation has not been established. *In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir. 1994).

The Office Action refers to various sections of Mitsuhashi arguing that the above steps are disclosed in the reference at column 14, lines 25-42, column 15, lines 16-60 and Figure 4. Applicant submits that neither the cited passages nor any other passages of the reference teaches the steps of forming clusters and selecting for a cluster a hybridization oligonucleotide probe. The cited passages indicate that Mitsuhashi provides a graphic display of all of the hybridizations of probes for a target mRNA with all sequences in the preparation. In other words, the reference teaches a graphic display of all of the candidate probes and their hybridization strengths with all sequences from the sequence database. The user is allowed to see visually the number of false hybridizations at various temperatures for all candidate probes and the sources of these false hybridizations. For each melting temperature of interest, a graphical representation of the number of hybridizations for each probe is displayed.

Within a window, a cursor shape is changed from a vertical line bisecting the screen to a small rectangle when the user selects a particular probe.

As can be seen, Mitsuhashi's method uses all of the hybridization probes for a target and further uses a number of hybridizations for each of all of the probes at a number of melting temperatures. The results are displayed graphically so that the user can observe the results from all of the hybridizations and using a cursor select a particular probe.

As Applicant indicated previously, the present methods are based on Applicant's discovery of forming clusters and selecting for a cluster hybridization oligonucleotides where hybridization of a hybridization oligonucleotide is predicted by the presence of the oligonucleotide in the cluster. Applicant's claimed methods reflect this discovery in that the claims recite the step of selecting, for a cluster, a hybridization oligonucleotide wherein the hybridization of the hybridization oligonucleotide is predicted by the presence of the hybridization oligonucleotide in the cluster.

Referring, for example, to Claim 1 as a typical claim, Claim 1 recites that a predetermined number of non-identical oligonucleotides within a nucleotide sequence that is hybridizable with the target nucleotide sequence is identified. The oligonucleotides are chosen to sample a length of the nucleotide sequence. For each of the oligonucleotides at least one parameter that is predictive of the ability of each of the oligonucleotides to hybridize to the target nucleotide sequence is determined and evaluated. A subset of oligonucleotides within the predetermined number of non-identical oligonucleotides is selected based on an examination of the parameter. Then, oligonucleotides in the subset are identified that are in clusters along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. A hybridization oligonucleotide is selected from a cluster where the hybridization of the hybridization oligonucleotide is predicted by the presence of the oligonucleotide in the cluster. The present invention avoids the evaluation of every probe in a probe set at multiple melting temperatures as carried out by Mitsuhashi.

The above may be better understood, for example, with reference to pages 46-49 of the present Specification. On the basis of the parameters of T_m and ΔG_{MFOLD}, certain oligonucleotides at various positions along the nucleotide sequence complementary to target nucleotide sequence were rejected (shown with lines drawn through in the parameter columns). The remaining oligonucleotides are examined for clustering. On page 49, a cluster is shown having 13 contiguous oligonucleotides. As

indicated on page 49, lines 4-5, any or all of the oligonucleotides in this cluster may be evaluated experimentally. Accordingly, in the above example, after the oligonucleotides are filtered according to predetermined parameter values, some oligonucleotides remain and others are rejected. The remaining oligonucleotides are viewed according to order of position along the nucleotide sequence and clusters of oligonucleotides are identified. In accordance with aspects of the invention, oligonucleotides that fall within the clusters are the ones of choice for further evaluation as hybridization probes. As mentioned earlier, Applicant has discovered that for the most part the clusters tend to contain oligonucleotides that exhibit good hybridization to a target sequence as compared to oligonucleotides that are not in clusters.

As a result of the present invention, only a fraction of the potential oligonucleotide probe candidates are synthesized and tested. This is in sharp contrast to the known method of synthesizing and testing all or a major portion of potential oligonucleotide probes for a given target sequence (Specification, page 42, lines 28). Such an approach is particularly important in the area of array analysis of target nucleotide sequences. As explained in the Specification (page 5, lines 17-28), oligonucleotide arrays can contain hundreds of thousands of different sequences and conditions are chosen to allow the oligonucleotide with the lowest melting temperature to hybridize efficiently. These conditions are usually relatively non-denaturing and secondary structure constraints become significant. Arrays are generally utilized under relatively non-denaturing conditions in contrast to, for example, PCR conditions, which tend to be strongly denaturing.

The present invention seeks to select good probes without performing full thermodynamic and other studies and without evaluating all probes. Applicant has found that good probes can be obtained by viewing clustering of a multitude of probes along a region of a nucleotide sequence that is hybridizable to the target nucleotide sequence where the efficiency of a hybridization probe is related to the size of the cluster.

Rejection under 35 U.S.C. §103

Claims 1, 5, 7, 9, 15-18, 20, 21 and 98-1-1 were rejected under paragraph (a) of the above code section as being unpatentable over Mitsuhashi in view of Southern (U.S. Patent No. 5,700,637). The Office Action argues that it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice Mitsuhashi

with Southern to utilize the computer programs as an efficient method to design optimal oligonucleotide probe sequences based on thermodynamic hybridizability, and transferring the resultant identified oligonucleotide probes to an oligonucleotide array manufacturing system.

Mitsuhashi is deficient in not disclosing or suggesting forming clusters and selecting a hybridization oligonucleotide wherein the hybridization of the hybridization oligonucleotide is predicted by the presence of the hybridization oligonucleotide in the cluster. Southern does not cure these deficiencies because Southern does not disclose or suggest such a feature. Furthermore, the combined teachings of Mitsuhashi and Southern do not suggest this feature of the claimed invention since neither reference teaches this element of the present claims. Accordingly, the presently claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made.

Objection to Claims

Claims 2-4, 6, 8, 10-14, 19, 22-27 and 30-40 were objected to as being dependent upon a rejected base claim but were indicated to be allowable if rewritten in independent form including all of the limitation of the base claim and any intervening claims. In view thereof, Claims 102-147 were added and are based on the objected to claims as pointed out in the "The Amendment" section above.

Conclusion

Claims 1-25, 27-40 and 98-147 satisfy the requirements of 35 U.S.C. §§112, 102 and 103. The Examiner has already approved a Terminal Disclaimer. Allowance of the above-identified patent application, it is respectfully submitted, is in order.

Respectfully submitted,

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